Anesthesiology 2008; 108:87–93

Persistent Depression of Contractility and Vasodilation with Propofol but Not with Sevoflurane or Desflurane in Rabbits

Colin Forbes Royse, M.D., B.S., David F. L. Liew,† Christine E. Wright, Ph.D.,‡ Alistair G. Royse, M.D., B.S.,‡ James A. Angus, Ph.D.§*

Background: **Propofol, sevoflurane, and desflurane may cause hemodynamic compromise during anesthesia and critical care management. The aim of the study was to compare these anesthetics during increased dose and recovery to maintenance level.**

Methods: **Anesthetized, open-chest New Zealand White rabbits were used to acquire dose–response curves with sevoflurane, desflurane, and propofol, followed by reduction to baseline infusion. Simultaneous high-fidelity left ventricular pressure and volume data were acquired during caval occlusion with a dual-field conductance catheter inserted *via* an apical stab. The preload recruitable stroke work and the end-diastolic pressure–volume relationship were used as the primary measures of contractility and diastolic function.**

Results: **The time-matched controls were stable over time. Propofol and desflurane but not sevoflurane caused dose-dependent reductions in myocardial contractility, although sevoflurane reduced contractility more at 1 minimal alveolar concentration. All anesthetics reduced mean arterial pressure, and significant recovery occurred for sevoflurane and desflurane but not for propofol. The end-diastolic pressure–volume relationship was increased by sevoflurane. Ejection fraction decreased with sevoflurane only. All anesthetics caused dose-dependent vasodilation, with recovery for desflurane and sevoflurane but not propofol. Heart rate was decreased with propofol without significant recovery. Propofol plasma concentrations remained elevated after dose return to baseline infusion rate, suggestive of distribution compartment saturation.**

Conclusion: **All three anesthetics caused dose-dependent decreases in cardiovascular function. Recovery of cardiovascular function occurred rapidly with sevoflurane and desflurane, but persistent depression of contractility, vasodilation, mean arterial pressure, and heart rate occurred with propofol during a 30-min recovery period.**

PROPOFOL, sevoflurane, and desflurane are commonly used agents for maintenance of general anesthesia in humans, and propofol is commonly used for sedation in the critical care environment. The volatile anesthetics are attractive agents for sedation because they are easily titrated with rapid emergence, but they require specialized delivery and scavenging systems, limiting their current use in the intensive care environment. These drugs are popular general anesthetics for a number of reasons including relatively rapid onset and offset of anesthesia,[1–3] and they are considered to have relatively few side effects. However hypotension and vasodilation are common associated cardiovascular sequelae.[4–6]

Because most anesthetic agents have both myocardial depressant and vasodilator properties, it is difficult to separate myocardial from vascular effects using ejection phase indices of systolic function (such as cardiac output or ejection fraction). It is imperative that a load-independent measurement of contractility and diastolic function be performed using pressure–volume loop technology, most commonly *via* integrated pressure and conductance catheters.[7] As these are highly invasive measurements, human data are rare.

The aims of this study were to compare the myocardial and vascular effects of propofol, sevoflurane, and desflurane during increased doses and during recovery to maintenance levels, using pressure–volume loops to identify myocardial *versus* vascular effects, to assess the effect on diastolic function and to determine differences among agents.

Materials and Methods

The study was approved by The University of Melbourne Animal Ethics Committee in accordance with the guidelines of the National Health & Medical Research Council of Australia.

New Zealand White rabbits (2.5–4.0 kg) were induced with propofol (10–50 mg/kg) *via* an indwelling ear vein catheter and then intubated and mechanically ventilated. Fluid-filled catheters were inserted into the right internal jugular vein and advanced into the right atrium and the right carotid artery. The heart was exposed *via* median sternotomy. An ultrasonic flow probe was placed around the ascending aorta (T206, Transonic Systems Inc., Ithaca, NY) to measure cardiac output. A 3-French combined micromanometer pressure and dual-field conductance catheter (SPR-855, Millar Instruments, Houston, TX) was inserted into the left ventricle *via* an apical stab. A silicone sling was placed around the inferior vena cava for acute preload reduction at each measurement time point. The phrenic nerves were divided to minimize the respiratory effect. Pressure–volume loops were recorded with a CFL-512 cardiac function laboratory (CD Leycom,

* Associate Professor, Anaesthesia and Pain Management Research Unit, and Cardiovascular Therapeutics Unit, Department of Pharmacology, University of Melbourne, Victoria, Australia. † Medical Student, ‡ Associate Professor, § Dean, Cardiovascular Therapeutics Unit, Department of Pharmacology, University of Melbourne.

Received from the Cardiovascular Therapeutics Unit, Department of Pharmacology, University of Melbourne, Victoria, Australia. Submitted for publication July 5, 2007. Accepted for publication August 23, 2007. Supported in part by a grant from Baxter Australia (Sydney, NSW, Australia) and from departmental sources.

Address correspondence to Dr. C. F. Royse: Department of Pharmacology, University of Melbourne, Victoria, 3010 Australia. colin.royse@unimelb.edu.au.

Zoetermeer, The Netherlands); details of use and calibration have been previously described.[8]

Load-independent data consisted of preload recruitable stroke work (PRSW) as a measurement of contractility. The PRSW is the slope of the stroke work/end-diastolic pressure–volume relationship (mmHg) obtained from the first 10–15 loops after acute preload reduction. An r^2 value >0.9 was used to determine an acceptable linearity of the PRSW measurement. The end-diastolic pressure–volume relationship was obtained from the first 10-15 loops after preload reduction as a measurement of diastolic function (chamber compliance). Other primary data included heart rate, mean arterial pressure (MAP), right atrial pressure, and cardiac output. Ejection fraction, systemic vascular resistance index, and cardiac index (cardiac output/body weight [$l \cdot min^{-1} \cdot kg^{-1}$]) were calculated.

Four groups were studied: a time-matched control group received desflurane at 8.9% for the duration of the study, and dose–response protocols were performed for propofol, sevoflurane, and desflurane, followed by return to baseline anesthetic rates for 30 min. Minimal anesthetic concentration (MAC) doses for rabbits: desflurane 8.9%,[9] sevoflurane 3.7%,[10] and propofol (equivalent level of anesthesia to 1 MAC) 70 mg $\cdot$ $kg^{-1} \cdot h^{-1}$ (1.15 mg $\cdot$ $kg^{-1} \cdot min^{-1}$).[11–13] The volatile anesthetics were delivered using an anesthetic machine and calibrated vaporizer using a T-piece circuit. The anesthetic dose was titrated to achieve the desired end-tidal concentrations, which were measured at the tip of the endotracheal tube. Propofol 1% solution was infused iv, and an equivalent volume of 0.9% NaCl was infused iv to animals in the volatile anesthetic groups.

Although anesthesia was induced with propofol, the anesthetic was changed once intubation and ventilation were commenced in the volatile anesthetic groups. Anesthesia was adjusted according to need during surgical preparation, then returned to baseline levels for a 30-min stabilization period before baseline recordings. Deep paw pinch was used to test depth of anesthesia at regular intervals, and the anesthetic was increased if there was any movement to surgical stimulation (during the recording phase no animals required an increased dose). The surgical preparation and stabilization period was typically 1.5 h, allowing a considerable wash-out period from the induction dose of propofol. The animals were kept normothermic (39°C) using a heated pad regulated by a rectal temperature probe. Ventilation was increased ($Paco_2$ <30 mmHg) to reduce spontaneous respiratory effort as muscle relaxants were not permitted by the ethics committee (pressure–volume loop recording requires apnea); pH was maintained at >7.3 and Fio_2 = 1 was used.

For the dose–response protocol, the anesthetic dose was increased at 10-min intervals, from 1 to 1.5 then twofold, followed by return to baseline levels for 30 min. We administered 0.9% NaCl iv so that the total volume infusion was 60 ml/h. Measurements were acquired 10 min after each change of dose and every 10 min during the recovery period.

A follow-up study was conducted to measure propofol plasma concentrations to identify whether observed cardiovascular changes were aligned with plasma levels. Two groups of rabbits (n = 3) were induced with propofol as described, intubated and ventilated, and commenced on an infusion of 70 mg $\cdot$ $kg^{-1} \cdot h^{-1}$. An arterial catheter was placed into an ear artery for measurement of MAP and to withdraw blood samples for propofol analysis. No additional surgery was performed. After 60 min, the dose–response group received an incremental infusion according to the protocol outlined, whereas the time control group received a constant infusion rate of 70 mg $\cdot$ $kg^{-1} \cdot h^{-1}$ for the duration of the experiment. Propofol assays were performed postinduction: 30 and 60 min later, 10 min after each dose increment, and every 10 min thereafter for 30 min. Blood samples for the propofol assay were collected in heparinized tubes and refrigerated at 4°C. Propofol blood concentrations decrease less than 0.2% per week at 4°C. They were subsequently analyzed using a high-performance liquid chromatography assay, modified from the method of Plummer.[14] This assay is linear to the least 20 mg/l and has a detection limit of 0.025 mg/l and coefficient of variation of 4.1% at 2 mg/l.[15]

Statistics

Data are presented graphically as dose–response curves and recovery for each variable (error bars ± within-subject SEM). For dose–response experiments and recovery phases, the difference in profile between the drug and time control groups was tested by repeated-measures analysis of variance using the Greenhouse-Geisser correction.[16] $P < 0.05$ was considered statistically significant. Differences in baseline values between drug and time control groups were tested by one-way analysis of variance. Analysis was performed on the raw data using SPSS version 12 (SPSS Inc., Chicago, IL). The sample size (n = 8–10) determination was based on detecting a 20% difference between the primary endpoint of PRSW (two-tailed $P = 0.05$, power 0.8) and a time control group and is consistent with pressure–volume loop studies in our laboratory, requiring 6–10 per group to identify significant differences among groups.[8,17]

Results

Eleven experiments were conducted for each group. In this model, 35 of 44 experiments were suitable for use. Failed experiments meant that they did not reach conclusion because of either an experimental mishap or equipment failure. The pressure–volume loop failures included excessive respiratory effort making the pressure–volume loops uninterpretable or catheter failure. One animal had a

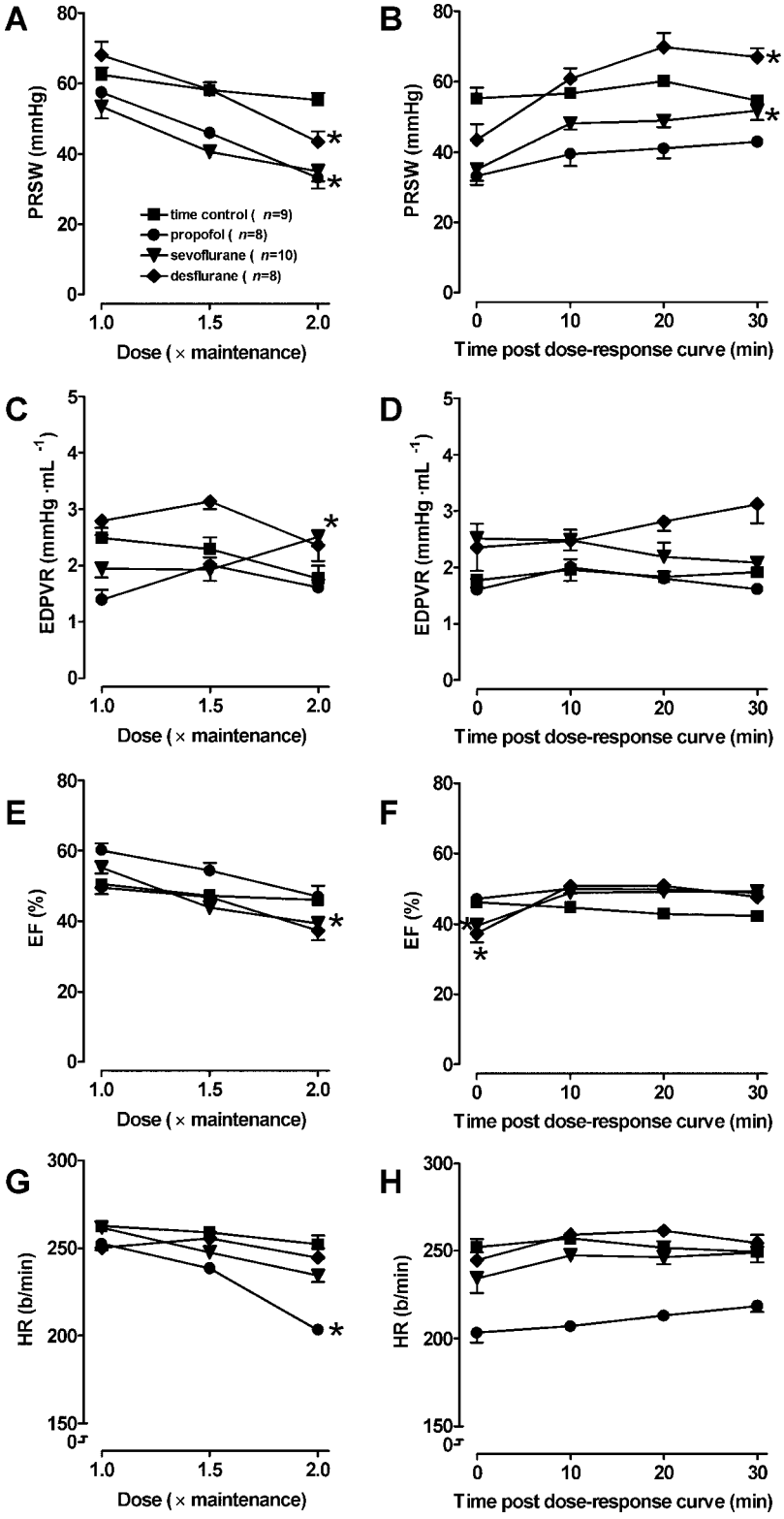

Fig. 1. Dose–response and recovery curves for myocardial variables: (*A*) preload recruitable stroke work (PRSW) dose–response and (*B*) recovery; (*C*) end-diastolic pressure–volume relationship (EDPVR) dose–response and (*D*) recovery; (*E*) ejection fraction (EF) dose–response and (*F*) recovery; (*G*) heart rate (HR) dose–response and (*H*) recovery for anesthetic doses 1, 1.5, and 2 times the maintenance levels at 10-min intervals and after return to dose × 1 for 30 min. Error bars are ± 1 SEM. *$P < 0.05$ using repeated-measures analysis of variance compared with the time control group.

very low blood pressure after induction of unknown cause and was killed before further surgery. The myocardial variables (PRSW, end-diastolic pressure–volume relationship, ejection fraction, and heart rate) are shown in figure 1, and the vascular variables (systemic vascular resistance index and MAP) are shown in figure 2.

Contractility (PRSW)

Compared with the time control group, there was a significant dose-dependent reduction in contractility for propofol ($P < 0.014$) and desflurane ($P = 0.032$) but not for sevoflurane ($P = 0.158$). Sevoflurane had the lowest value of contractility at baseline, but there were no signif-

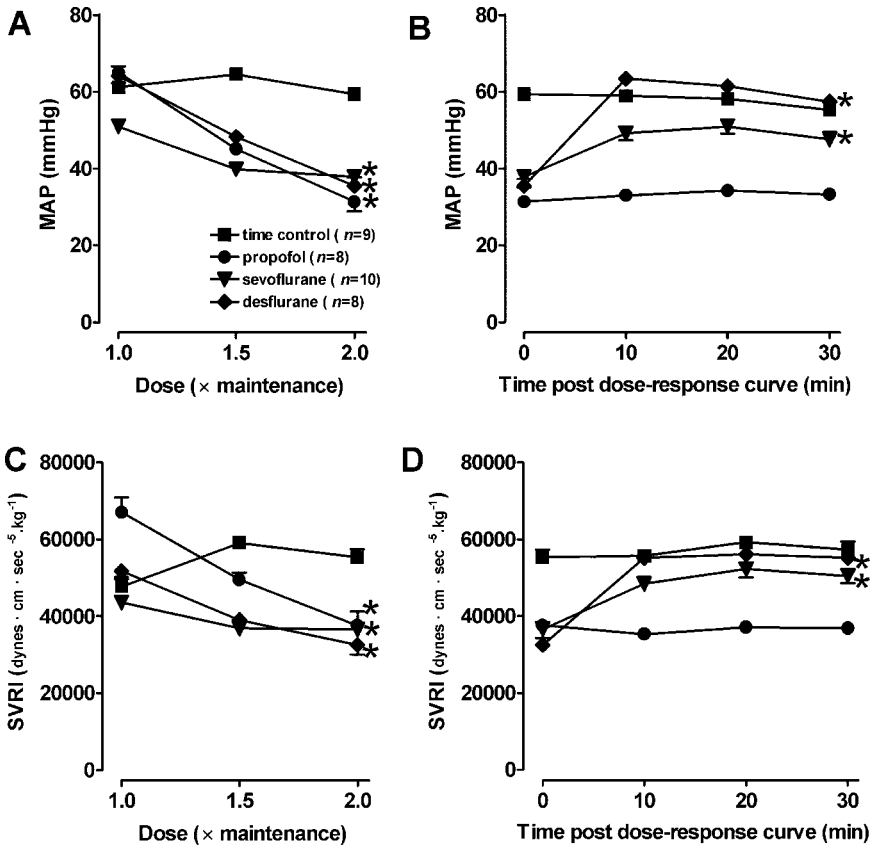

Fig. 2. Dose–response and recovery curves for vascular variables: (*A*) mean arterial pressure (MAP) dose–response and (*B*) recovery; and (*C*) systemic vascular resistance index (SVRI) dose–response and (*D*) recovery for anesthetic doses 1, 1.5, and 2 times the maintenance levels at 10-min intervals and after return to dose × 1 for 30 min. Error bars are ± 1 SEM. *$P < 0.05$ using repeated-measures analysis of variance compared with the time control group.

icant differences among groups at baseline (all $P > 0.05$). During recovery from 2 MAC to 1 MAC, both sevoflurane ($P = 0.036$) and desflurane ($P = 0.010$) showed significant recovery of contractility compared with the time-matched controls. In contrast, propofol did not return to baseline values ($P = 0.26$).

Chamber Stiffness (End-Diastolic Pressure–Volume Relationship)

There were no significant dose-dependent effects on chamber stiffness for propofol or desflurane, but sevoflurane caused a significant increase ($P = 0.015$). At baseline, sevoflurane had the lowest value for end-diastolic pressure–volume relationship, which was significantly different from control ($P = 0.027$).

Mean Arterial Pressure

There was a significant dose-dependent decrease in MAP for all anesthetics (all $P < 0.001$). At baseline, the MAP was significantly lower for sevoflurane than for the other groups ($P = 0.04$). During recovery, sevoflurane ($P = 0.007$) and desflurane ($P < 0.001$) showed significant recovery compared with the time-matched control, whereas there was no significant recovery with propofol ($P = 0.21$).

Systemic Vascular Resistance Index

Dose-dependent vasodilation was caused by all anesthetics: propofol ($P < 0.001$), desflurane ($P < 0.001$), and sevoflurane ($P = 0.001$). During recovery, desflurane ($P < 0.001$) and sevoflurane ($P = 0.03$) showed significant recovery compared with the time-matched controls, whereas there was no recovery with propofol ($P = 0.56$).

Heart Rate

Propofol caused dose-dependent decreases in heart rate ($P = 0.001$), whereas there was no effect with sevoflurane ($P = 0.149$) or desflurane ($P = 0.568$). During recovery there were no significant changes compared with the time-matched controls for any of the drugs (all $P > 0.05$).

Ejection Fraction

Dose-dependent reductions in ejection fraction were caused by sevoflurane ($P = 0.018$) but not by propofol ($P = 0.157$) or desflurane ($P = 0.067$). Significant recovery occurred with sevoflurane ($P < 0.001$) and desflurane ($P < 0.001$) compared with the time-matched controls, and they remained unchanged for propofol ($P = 0.31$).

Propofol Assays

At an infusion of 70 mg · kg^{-1} · h^{-1}, the level of anesthesia was light. There was no spontaneous movement or reaction to paw pinch, but nystagmus was common and movement was observed to manipulation

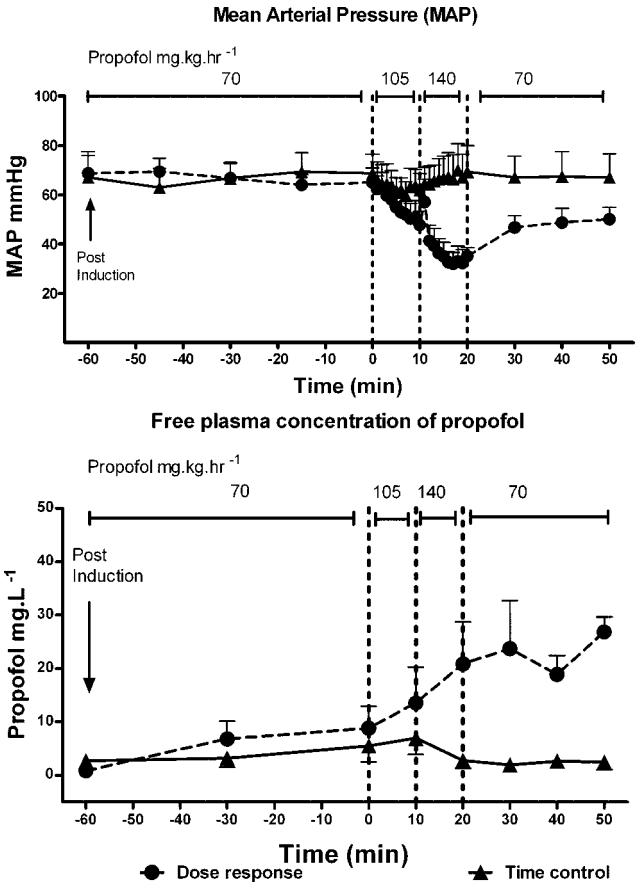

Fig. 3. Mean arterial pressure and free plasma propofol concentrations for time control and dose–response rabbits (n = 3 each). Animals were anesthetized but did not undergo sternotomy. Error bars are ± 1 SEM.

of the endotracheal tube. In the dose–response group, the animals would not move even with tracheal manipulation once the propofol dose was increased; this persisted for the rest of the experiment. In the control group, the MAP was constant over time, as were the propofol concentrations (range, 2.5-5.5 mg/l). In the dose–response group, the MAP showed the same decline as in the pressure–volume loop experiments. The propofol concentrations increased in proportion to the dose (mean 8.8 mg/l at 70 mg · kg^{-1} · h^{-1}, 13.5 mg/l at 105 mg · kg^{-1} · h^{-1}, and 20.8 mg/l at 140 mg · kg^{-1} · h^{-1}) but remained elevated after reduction of the infusion to baseline levels (fig. 3).

Discussion

The major finding of this study was that doubling the maintenance dose of propofol, sevoflurane, and desflurane caused dose-dependent depression of myocardial contractility (for propofol and desflurane but not sevoflurane), decrease in MAP, and peripheral vasodilation. On returning the anesthetic doses to maintenance level, the offset of the depression of contractility, hypotension, and peripheral vasodilation was complete within 30 min for the volatile agents but not for propofol. The mechanism of the prolonged cardiovascular depression is pharmacokinetic, as the plasma concentrations of propofol remained elevated after the infusion rate was returned to baseline values, suggestive of zero-order kinetics and distribution compartment saturation.

Propofol, sevoflurane, and desflurane have all been shown to have significant cardiovascular effects.[4–6] This study is the first to compare the hypotensive effects of all three drugs in one test series using pressure–volume loops. These results show dose-dependent hypotension caused by a simultaneous depression of contractility and vasodilation. This supports previous studies that showed a dose-dependent decrease in blood pressure with propofol[18] and depression of contractility measured by PRSW.[19]

Significant dose-dependent decline of PRSW was observed for propofol and desflurane. The baseline value of MAP at 1 MAC or its equivalent was lower for sevoflurane compared with the other groups, and the maximal depression of contractility was equivalent to that of propofol and desflurane. This raises the question of whether the degree of depression at 1 MAC may be different among drugs. The dose–response curves may not be linear, with the proportion of maximal depression occurring at a given dose differing among anesthetics. This may be the result of different levels of compensatory sympathetic outflow and/or baroreceptor depression at equi-anesthetic doses.

Propofol caused a decrease in heart rate with increased dose. This is consistent with studies by Brussel *et al.* and Cullen *et al.*[20,21] Neither sevoflurane nor desflurane showed any significant changes in heart rate with increasing doses, which is contrary to the findings of Ebert *et al.*,[22] in whose study hypertension and tachycardia occurred in young people at 1.5 MAC desflurane. Passive diastolic function was unaffected by propofol and desflurane but worsened with sevoflurane. Yamada *et al.*[23] similarly found a dose-dependent worsening of passive diastolic function with sevoflurane. Ejection fraction was not significantly decreased by propofol or desflurane, which highlights the problem of using ejection phase indices of systolic function when the drug in question has both myocardial depressant and vasodilator properties. Vasodilation improves ejection fraction and thereby masks the effects of decreased contractility.

In this study, cardiovascular function returned rapidly to baseline values with sevoflurane and desflurane but not with propofol. Desflurane recovery was faster than sevoflurane, consistent with its more rapid elimination.[24,25] Propofol, however, did not show significant recovery of contractility, vascular resistance, MAP, or heart rate. The follow-up study was performed to identify whether the prolonged cardiovascular depression was caused by elevated plasma concentrations. Anes-

thetic doses in rabbits are different from those in humans, with rabbits requiring a higher dose (this is especially the case for propofol, for which the doses used are considerably higher). This study used published values for MAC for sevoflurane[10] and desflurane[9] in rabbits and an estimate for equi-anesthetic maintenance levels of propofol based on three rabbit studies[11–13] and the experience of this laboratory. Plasma concentrations for the time control were relatively constant during the study and in a range consistent with human plasma levels (2.5–5.5 mg/kg), despite a higher infusion rate than that used in humans. The light plane of anesthesia exhibited in the animals was consistent with a MAC level of anesthesia. The propofol concentration increased proportionally at the end of each 10-min dose increment but remained elevated when the infusion rate was decreased. The delayed return of cardiovascular parameters was therefore appropriate for the plasma concentrations. In contrast, end-tidal concentrations of desflurane and sevoflurane returned to baseline values rapidly after reducing the concentration to 1 MAC.

The clinical implications of our study are that there are dose-dependent cardiac effects and vascular effects with all three anesthetics, with a similar magnitude of effect at double the maintenance dose. Plasma propofol concentrations were proportionally elevated at the end of each 10-min dose escalation. All three drugs caused vasodilation and decreased contractility, although the change in contractility with the increase from 1 to 2 MAC with sevoflurane may be less than that for desflurane or propofol. Decreased heart rate may be clinically important with propofol at higher doses. Persistent cardiovascular depression with propofol was a surprising finding, as was the mechanism of persistently elevated plasma concentrations after the infusion rate was reduced. This meant that there was a failure of rapid redistribution of the drug to inactive compartments consistent with saturation of those compartments. The rabbits were young and lean and may therefore have smaller redistribution compartments. Furthermore, the dose required to maintain anesthesia was large on a weight basis compared with a human, which could lead to more rapid saturation of compartments. The plasma concentrations measured in this study, however, were in a range similar to concentrations in humans for propofol when used as a sole agent. Andrews *et al.*[15] reported plasma propofol concentrations for preventing movement to breast incision in healthy patients. The CP_{50} at which 50% of patients moved was 14.3 ± 1.6 mg/l, and CP_{95} was 20.6 mg/l. The MAP at each respective concentration was 63 ± 4 and 43 mmHg, indicating clinically important hypotension at higher doses.

These findings raise several questions. Could the finding of persistently elevated plasma propofol concentrations occur in humans after a prolonged infusion for major surgery or sedation? Could compartment saturation occur in particular patient groups such as young children, the elderly, or those with reduced body mass index, and lead to elevated plasma concentration after prolonged or high-dose infusions? Is it possible that compartment saturation is a precursor to the propofol infusion syndrome? Unfortunately, there are very few clinical studies in which propofol concentrations have been measured after long-term intensive care unit sedation or after prolonged operations such as cardiac surgery. Rigby-Jones *et al.*[26] measured propofol concentrations in children who were sedated in the intensive care unit (they had not received propofol for anesthesia) and found variability in the kinetics and concentrations achieved, unacceptable hypotension in 2 of 20 patients, and increasing metabolic acidosis in 1 patient. Very small babies and patients who underwent cardiac surgery demonstrated reduced clearance. Knibbe *et al.*[27] measured propofol concentrations in 20 intensive care unit patients sedated for up to 5 days and found intraindividual variation in both pharmacokinetics and pharmacodynamics. Further research is required on larger patient samples to identify whether persistently elevated plasma concentrations of propofol can occur in humans, in what proportion of patients, and in which patient groups they are most likely to occur. The use of low-solubility volatile anesthetics may be favorable for prolonged surgical procedures and intensive care sedation.

There are several limitations in this study. This study was conducted in healthy rabbits, and the observed effects may not necessarily predict human outcomes. The preparation in this study, however, is representative of major surgery and decreases the confounders of patient comorbidities, and the use of pressure–volume loops allows separation of myocardial from vascular effects. The use of propofol to induce anesthesia is unlikely to cause a significant interaction with the other anesthetics tested as induction involved a small bolus dose with a long period (approximately 1.5 h) to washout before baseline recordings. On a weight basis, the amount of propofol required to maintain anesthesia seems high compared with humans, although plasma concentrations are similar for humans when propofol is used as a sole agent.[15] Other investigators have used lower propofol doses, but not as a sole agent, thereby decreasing the dose required to maintain anesthesia (propofol 36 $mg \cdot kg^{-1} \cdot h^{-1}$ with buprenorphine[28]; 48 $mg \cdot kg^{-1} \cdot h^{-1}$ with ketamine and fentanyl[29]; or 36 $mg \cdot kg^{-1} \cdot h^{-1}$ with ketamine, xylazine, fentanyl, and vecuronium[30]).

Conclusion

All three anesthetics caused dose-dependent decreases in cardiovascular function. Recovery of cardiovascular function occurred rapidly with sevoflurane and desflu-

rane, but persistent depression of contractility, MAP, heart rate, and vasodilation occurred with propofol during a 30-min recovery period because of persistently elevated plasma concentrations.

The authors thank Linda Cornthwaite-Duncan, Catherine Jones, and Karen Groves (Research Assistants, Cardiovascular Therapeutics Unit, Department of Pharmacology, University of Melbourne, Victoria, Australia) for their technical assistance. The authors also thank Andrew Bjorksten, Ph.D. (Senior Scientist, Department of Anaesthesia and Pain Management, The Royal Melbourne Hospital, Melbourne, Australia), who kindly performed the propofol assays.

References

1. Yasuda N, Lockhart SH, Eger EI II, Weiskopf RB, Liu J, Laster M, Taheri S, Peterson NA: Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 1991; 72:316–24

2. Yasuda N, Lockhart SH, Eger EI II, Weiskopf RB, Johnson BH, Freire BA, Fassoulaki A: Kinetics of desflurane, isoflurane, and halothane in humans. ANESTHESIOLOGY 1991; 74:489–98

3. Dutta S, Ebling WF: Emulsion formulation reduces propofol's dose requirements and enhances safety. ANESTHESIOLOGY 1997; 87:1394–405

4. Ebert TJ, Harkin CP, Muzi M: Cardiovascular responses to sevoflurane: A review. Anesth Analg 1995; 81:S11–22

5. Nathanson MH, Fredman B, Smith I, White PF: Sevoflurane *versus* desflurane for outpatient anesthesia: a comparison of maintenance and recovery profiles. Anesth Analg 1995; 81:1186–90

6. Claeys MA, Gepts E, Camu F: Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988; 60:3–9

7. Baan J, van der Velde ET, Steendijk P: Ventricular pressure-volume relations *in vivo* Eur Heart J 1992;13(suppl E):2–6.

8. Royse CF, Royse AG: The myocardial and vascular effects of bupivacaine, levobupivacaine, and ropivacaine using pressure volume loops. Anesth Analg 2005; 101:679–87

9. Doorley BM, Waters SJ, Terrell RC, Robinson JL: MAC of I-653 in beagle dogs and New Zealand white rabbits. ANESTHESIOLOGY 1988; 69:89–91

10. Scheller MS, Saidman LJ, Partridge BL: MAC of sevoflurane in humans and the New Zealand white rabbit. Can J Anaesth 1988; 35:153–6

11. Van Leeuwen AF, Evans RG, Ludbrook J: Effects of halothane, ketamine, propofol and alfentanil anaesthesia on circulatory control in rabbits. Clin Exp Pharmacol Physiol 1990; 17:781–98

12. Watts AD, Eliasziw M, Gelb AW: Propofol and hyperventilation for the treatment of increased intracranial pressure in rabbits. Anesth Analg 1998; 87: 564–8

13. Perez-Martinez A, Gonzalvez-Pinera J, Marco-Macian A, Carpintero-Moreno F, Moya-Marchante M,: [Propofol in continuous perfusion as anesthetic in experimental surgery in the rabbit]. Rev Esp Anestesiol Reanim 1995; 42:253–6

14. Plummer GF: Improved method for the determination of propofol in blood by high-performance liquid chromatography with fluorescence detection. J Chromatogr 1987; 421:171–6

15. Andrews DT, Leslie K, Sessler DI, Bjorksten AR: The arterial blood propofol concentration preventing movement in 50% of healthy women after skin incision. Anesth Analg 1997; 85:414–9

16. Ludbrook J: Multiple comparisons procedures updated. Clin Exp Pharmacol Physiol 1998; 25:1032–7

17. Royse CF, Royse AG, Rohrlach R, Wright CE, Angus JA: The cardiovascular effects of adrenaline, dobutamine and milrinone in rabbits using pressure-volume loops and guinea pig isolated atrial tissue. Anaesth Intensive Care 2007; 35:180–8

18. Ebert TJ: Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. ANESTHESIOLOGY 2005; 103:20–4

19. Pagel PS, Warltier DC: Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. ANESTHESIOLOGY 1993; 78:100–8

20. Brussel T, Theissen JL, Vigfusson G, Lunkenheimer PP, Van Aken H, Lawin P: Hemodynamic and cardiodynamic effects of propofol and etomidate: Negative inotropic properties of propofol. Anesth Analg 1989; 69:35–40

21. Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J: Effect of propofol anesthesia on baroreflex activity in humans. Anesth Analg 1987; 66:1115–20

22. Ebert TJ, Muzi M: Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers: A comparison with isoflurane. ANESTHESIOLOGY 1993; 79: 444–53

23. Yamada T, Takeda J, Koyama K, Sekiguchi H, Fukushima K, Kawazoe T: Effects of sevoflurane, isoflurane, enflurane, and halothane on left ventricular diastolic performance in dogs. J Cardiothorac Vasc Anesth 1994; 8:618–24

24. Eger EI II, Gong D, Koblin DD, Bowland T, Ionescu P, Laster MJ, Weiskopf RB: The effect of anesthetic duration on kinetic and recovery characteristics of desflurane *versus* sevoflurane, and on the kinetic characteristics of compound A, in volunteers. Anesth Analg 1998; 86:414–21

25. Yasuda N, Targ AG, Eger EI II: Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 1989; 69:370–3.

26. Rigby-Jones AE, Nolan JA, Priston MJ, Wright PM, Sneyd JR, Wolf AR: Pharmacokinetics of propofol infusions in critically ill neonates, infants, and children in an intensive care unit. ANESTHESIOLOGY 2002; 97:1393–400

27. Knibbe CA, Zuideveld KP, DeJongh J, Kuks PF, Aarts LP, Danhof M: Population pharmacokinetic and pharmacodynamic modeling of propofol for long-term sedation in critically ill patients: A comparison between propofol 6% and propofol 1%. Clin Pharmacol Ther 2002; 72:670–84

28. Martin-Cancho MF, Lima JR, Luis L, Crisostomo V, Carrasco-Jimenez MS, Uson-Gargallo J,: Relationship of bispectral index values, haemodynamic changes and recovery times during sevoflurane or propofol anaesthesia in rabbits. Lab Anim 2006; 40:28–42

29. Luo Y, Russell GB, Griffith JW, Lang CM: Comparison of anesthesia induced by ketamine-fentanyl combination and maintained by propofol or etomidate in New Zealand white rabbits. Lab Anim Sci 1995; 45:269–75

30. De Mulder PA, Van Kerckhoven RJ, Adriaensen HF, Gillebert TC, De Hert SG: Continuous total intravenous anesthesia, using propofol and fentanyl in an open-thorax rabbit model: evaluation of cardiac contractile function and biochemical assessment. Lab Anim Sci 1997; 47:367–75